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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,852	03/08/2001	Shu-Jen David Chiang	ON0163NP	6300

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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,852	CHIANG ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-11 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-11,14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 23, 2005 has been entered.

The AF amendment filed September 30, 2005 amending claims 3-6 and adding claims 14-16 has been entered.

Claims 1, 3-6, 8-11 and 14-16 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8-10 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-6, 8-10 and 14 are drawn to a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin esterase. Therefore, these claims recite a genus of nucleic acids encoding a *Rhodosporidium* cephalosporin esterase. This genus encompasses nucleic acids encoding any cephalosporin, including cephalosporin C, esterase from any species and strains of *Rhodosporidium.* Furthermore, said genus encompasses nucleic acids encoding esterases that hydrolyze the acetyl bond on the 10-position of a cephalosporin as well as other(s) position(s).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as be structure, formula [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase is represented by a genomic nucleic acid isolated from a single strain of *Rhodosporidium toruloides* (ATCC 10657) having the nucleotide sequence of SEQ ID NO:1 and corresponding cDNA having the sequence of SEQ ID NO:3. SEQ ID NOs: 1 or 3 encode cephalosporin C esterase of SEQ ID NO:2 that hydrolyzes the acetyl bond on the 10-position of cephalosporin C (Official name Cephalosporin-C deacetylase). No other nucleic acid sequences encoding a *Rhodosporidium* cephalosporin esterase are disclosed in the specification. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a *Rhodosporidium* cephalosporin esterase.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention, the genus of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase.

Claims 1, 3-6, 8-10 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase of SEQ ID NO:2, including SEQ ID NOs:1 and 3, does not reasonably provide enablement for a method of use of a strain of *Acremonium*

chrysogenum transformed with a nucleic acid encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NOs: 1 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claims which encompass nucleic acids having an unknown homology to SEQ ID NOs:1 or 3 and encoding any *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO: 2.

The specification does not teach nucleic acids encoding any *Rhodosporidium* cephalosporin C esterase other than the esterase having the amino acid sequence of SEQ ID NO: 2 encoded by SEQ ID NOs:1 or 3. While recombinant hybridization techniques are known, only highly homologous sequences can be identified using a given nucleic acid sequence. The state of the art provides no reasonable expectation of success in obtaining nucleic acid encoding *Rhodosporidium* cephalosporin esterase

having an unknown homology to SEQ ID NOs: 1 and the result of such screening is unpredictable.

Without sufficient guidance, beyond that provided, determination of nucleic acids encoding a *Rhodosporidium* cephalosporin C esterase having an unknown homology to SEQ ID NO:2, said nucleic acid having an unknown homology to SEQ ID NOs:1 or 3 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel vectors. Since the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available (e.g., page 31, lines 19-26, the sequence of an 1.2 kb fragment as well as sequences of plasmid A and plasmid pJB10 are unknown).

It is noted that Applicants have deposited *A. chrysogenum* comprising the DNA expression vector pBMesterase11 with ATCC on January 27, 1999 under the Budapest

Treaty but there is no indication in the specification as to public availability (specification, page 10, lines 14-19). An affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6, 8-11, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al in view of Politino et al. (A) or (B).

Smith et al. (US Patent 4,533,632, form PTO-1449 filed June 14, 2001, reference AC) teach a process for the conversion of cephalosporin C into desacetylcephalosporin C by fermenting cephalosporin C producing strain of *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides*. This process leads to "practically no loss of cephalosporin product due to decomposition" (column 1, lines 45-50). The process of fermentation is carried out at 15°-45° C and pH 4-9 (claims 1-7). Smith et al teach that fermentation is preferably carried out at about 25°C and pH 5-8 (column 3, lines 21-28).

Politino et al. (A), (US Patent 5,869,309, form PTO-1449 filed June 14, 2001, reference AG) is US counterpart of WO 98/12345Politino et al. (B), (WO 98/12345, form PTO-1449 filed January 14, 2002, reference AM).

The text below refers to US 5,869,309.

Politino et al. (A) teach a DNA encoding cephalosporin C esterase from *Rhodosporidium toruloides* that is 100% identical to SEQ ID NOs: 1 or 3 of the instant invention, a vector and a host cell comprising thereof, including *Cephalosporium acremonium* comprising thereof (claims 17-23). With regard to claim 14, they teach that "in a fungal cell system, the expression vectors should be contain promoters isolated from the genome of fungal cells (e.g., the cephalosporin esterase promoter from *R. toruloides* or the trpC promoter from *Aspergillus nidulans*)" (column 5, lines 26-30, 45-46). They teach the method for producing the cephalosporin C esterase by culturing cells of *Cephalosporium acremonium* transformed with a DNA encoding a cephalosporin esterase from *Rhodosporidium toruloides* (claim 24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use cephalosporin C producing strain of *Acremonium chrysogenum* transformed with a DNA encoding *R. toruloides* esterase for the production of desacetylcephalosporin C. One of ordinary skill in the art would have been motivated to use a cephalosporin C producing strain of *Acremonium chrysogenum* transformed with a DNA encoding *R. toruloides* esterase as opposed to adding the purified esterase to because this would obviate the need to produce, isolate and purify the enzyme which is time consuming and costly. One of ordinary skill in the art would

have a high expectation of success because *Acremonium chrysogenum* strain comprising DNA encoding *R. toruloides* esterase is taught by Politino et al. Furthermore, with regard to claim 8, it would have been further obvious to find and use optimal conditions for producing of desacetylcephalosporin C and fermenting *Acremonium chrysogenum* within the range of standard conditions taught by Smith et al. With regard to claims 1 and 3-6, one of ordinary skill in the art would have a reasonable expectation of the chemical breakdown of cephalosporin C of less than 40%, 30%, 20%, 10% or 5% in view of the teachings of Smith et al, *supra*. Thus, this is the expected property of the process that is obvious in view of the teachings of Smith et al and Politino et al. that was demonstrated by Applicants. The recitation of this property does not render the process non-obvious.

Response to Arguments

Applicant's arguments filed September 30, 2005 have been fully considered but they are not persuasive.

With regard to the 112, 1st written description rejection, Applicants argue that "Contrary to the Examiner's position, the specification thoroughly describes the claimed method of the invention. The specification teaches a process for directly producing desacetylcephalosporin C using a host cell containing recombinant nucleic acid having a sequence coding for all or part of cephalosporin esterase from *Rhodosporidium*. A representative (and preferred) source of the esterase nucleic acid is *Rhodosporidium toruloides* ATCC 10657 which is publicly available. See, for instance, page 3, line 29 to

page 4, line 3 of the specification. However, naturally occurring allelic variants of the esterase may be present in *Rhodosporidium* and these variants are within the scope of the claimed invention. See, for instance, page 4, line 20-25, of the specification, describing the existence of allelic variants. Methods of obtaining recombinant nucleic acid molecules are well-known in the art. For instance, genomic or CDNA libraries can be screened to identify sequences coding for all or part of the cephalosporin esterase. See, for instance, page 5, line 3 to page 6, line 23, of the specification, describing methods for obtaining nucleic acid sequences that encode the esterase. Various mutants of the nucleic acid sequence encoding the esterase are also within the scope of the invention. These mutations may be degenerate or non-degenerate. Such modifications can be prepared by intentionally mutating the cephalosporin DNA sequence so as to cause substitution, insertion, inversion, or addition of one or more amino acids in the encoded esterase polypeptide using techniques that are well-known in the art. See, for instance, page 6, line 24 to page 7, line 16; and page 13, line 9 to page 14, line 19, of the specification " (Remarks, page 7). These arguments are not persuasive because the point of the rejection is that the recited genus encompasses cephalosporin esterases acting not only on cephalosporin C but on other cephalosporins as well. Further, the subgenus of cephalosporin C esterases encompasses esterases that hydrolyze the acetyl bond on the 10-position of a cephalosporin C as well as other(s) position(s). Further, the recited genus of *Rhodosporidium cephalosporin* esterases encompasses said esterases from any species of *Rhodosporidium* and allelic variants thereof. The description of one allelic

variant does not allow to predict the structure of other allelic variants. With regard to the mutations methods, the arguments are not relevant to claimed invention that uses a naturally occurring esterase. Regardless of this, the description of a method of making the product does not substitute for the description of the product itself.

With regard to the 112, 1st enablement rejection, Applicants argue that "Methods of obtaining recombinant nucleic acid molecules are well known in the art" (page 9). While this is agreed to with regard to the sequences that are highly homologous to SEQ ID NOs: 1, 3, the arguments are not persuasive in relation to an esterase of any structure.

The 102 (b, e) rejections are withdrawn in view of Applicants remarks (pages 11-15). Furthermore, the method for producing a polypeptide having cephalosporin esterase activity taught by Politino et al comprises the step of isolating the expressed polypeptide that is not needed in the claimed process (US 5,869,309, claim 24).

With regard to the 103(a) rejection, Applicants argue that Smith describes a method of fermenting cephalosporin C-producing microorganisms, e.g., *Acremonium chrysogenum*, in the presence of added acetylesterase enzyme so that cephalosporin C formed is converted into desacetylcephalosporin C. See abstract. The acetylesterase, as a separate bioreagent, is added at some point during the fermentation process. See Smith at col. 2, lines 14-28; col. 3, lines 56-68. While Smith does describe conducting fermentation at 15-45°C and pH 4.9, such disclosure relates to a method involving addition of esterase enzyme into a fermentation broth containing a cephalosporin C-producing microorganism and is not a disclosure of a method for directly producing

desacetylcephalosporin C from a *Acremonium chrysogenum* strain having nucleic acid encoding cephalosporin biosynthesis enzymes and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase. Thus, Smith alone or in combination with Politino A or B is not prior art under 35 U.S.C §103(a) against the claims. Withdrawal of the §103(a) rejection is in order and is respectfully requested. The Applicants further submit that the § 103(a) rejection based on Politano A or B in view of Smith cannot be applied to reject new claims 14-16" (page 17). These arguments are not persuasive because as the references in the 103(a) rejection, neither Politino nor Smith has to disclose the same invention but only to make it obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
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Art Unit 1652